REMARKS

Reconsideration is requested.

Claims 1-23 and 25-33 have been canceled, without prejudice.

Claims 34-44 have been added and are supported by the specification. The polypeptide of ¶(b) in claim 24 has been made the subject of new claim 34, and claims 25-33 have been rewritten as new claims 35-43, respectively. The polypeptide of ¶(c) in claim 24 has been rewritten as new claim 44 which is dependent from new claim 43. Also, the formula (Ia) in claim 33 has been amended according to the formula (Ib) of ¶(c) in claim 24. No new matter has been added.

Claims 24 and 33-44 are pending.

A response to the Request of July 30, 2004 has not been received.

The Section 112, second paragraph, rejection of claims 24, 28 and 29 is believed to be obviated by the amendment to the preamble of claim 24. Withdrawal of the rejection is requested.

The Section 102 rejection of claims 24, 28 and 29 over U.S. Patent No. 5,824,778 (Ishikawa) is traversed. Reconsideration and withdrawal of the rejection are requested as the applicants believe that the cited patent fails to teach or suggest that an increase of platelet counts of a patient with decreased platelet counts are accelerated by the administration of a chemically modified G-CSF. The claims are submitted to be patentable over the cited art.

The Section 103 rejection of claims 24, 28 and 29 over "background art" or Tanikawa (presumably Experimental Hematology 17:883-888 (1989)) or WO 91/07988 or Koike (presumably AN 91:940291 Biosis (1991)) or Washizuka (presumably AN

92:197606 Medline (1992)), in view of Ono (U.S. Patent No. 5,342,940) or Ishikawa (U.S. Patent No. 5,824,778), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following, the attached and the evidence of record.

The present invention provides a method for increasing the platelet count of a patient with decreased platelet counts. The claimed method involved administration of a chemically modified hG-CSF. The claimed method, and the effect of the administration of the modified hG-CSF discovered by the applicants, would not have been expected by the ordinarily skilled person based on the combination of references cited by the Examiner.

Regarding Tanikawa, the Examiner is requested to see the Yamasaki Declaration executed on August 28, 1998 in the parent U.S. application No. 08/696,988, a copy of which was attached to the Amendment field May 20, 2004. The Declaration is found in the IFW of the USPTO PAIR grouped with the "Applicant Arguments or Remarks Made in an Amendment" filed May 20, 2004.

In the noted Declaration, intact-hG-CSF or chemically modified hG-CSF was administered to mice whose platelet counts were decreased by X-ray irradiation in the same manner as in Experimental example 2 in the present specification. The results are believed to clearly show that the platelet counts were remarkably increased in the mice to which the chemically modified hG-CSF was administered (▲, ■), on the 9th and 11th days after the start of the irradiation, in comparison with the untreated mice (♦). On the other hand, the platelet counts of the mice to which the intact-hG-CSF was administered (|, +) were lower than those of the untreated mice (♦), so that it was shown that un-modified hG-CSF has no activity of accelerating platelet counts.

Accordingly, even if one of ordinary skill in the art were motivated by the art to combine Tanikawa with Ono or Ishikawa disclosing PEGylated hG-CSF, which the applicants do not believe would have been the case, it is apparent that the presently claimed invention, which uses chemically modified G-CSF, provides an unexpected effect.

Regarding WO91/07988, Table 2 on page 18 shows that megakaryocyte colony formation which is an index of platelet increase was not found when G-CSF alone was administered to bone marrow cells. This result is believed to demonstrate that G-CSF has no activity for accelerating platelet counts. Accordingly, even if one of ordinary skill in the art were motivated by the art to combine WO91/07988 with Ono or Ishikawa disclosing PEGylated hG-CSF, which the applicants do not believe would have been the case, it is apparent that the presently claimed invention, which uses chemically modified G-CSF, provides an unexpected effect.

Regarding Koike (International Congress Series, 956, "Myelodysplastic Syndrome and Cytokines; International Symposium, Sapporo, Japan, September 28-29, 1990" pp289-292 (1991), Elsevier Science Publishers B.V.; a full copy of which is attached), Koike discloses at page 291, lines 10-14, that neither erythrocytes nor platelets increased by administration of rhG-CSF. This result demonstrates that G-CSF was expected to have no activity of accelerating platelet counts. Accordingly, even if one of ordinary skill in the art were motivated by the art to combine Koike with Ono or Ishikawa disclosing PEGylated hG-CSF, which the applicants do not believe would have been the case, it is apparent that the presently claimed invention, which uses chemically modified G-CSF, provides unexpected effect.

Regarding Washizuka (*Am. J. Hematol*, 39, 153-154 (1992), a full copy is attached along with the attached Appendix A which is a blowback copy of Fig. 1 of Washizuka in which arrows were added for emphases). At the points in May, 1989 (emphasized by "↑" in Fig. 1 of Appendix A) before the administration of hG-CSF, neither neutrophils nor RBC was increased, whereas the platelet counts were increased in comparison with the point in April, 1989 . Furthermore, in the term from June, 1989 to February 1990 in which hG-CSF was continuously administered, the platelet counts were gradually decreased, rather than increase, and the platelet counts at the start of the administration (the first occurrence "↓" for emphasis in Fig. 1 of Appendix A) are almost the same as those on January 1, 1990 (the second occurrence "↓" for emphasis in Fig. 1 of Appendix A). Additionally, after the second administration, the platelet counts were gradually decreased, although the dose was increased. This result demonstrates that G-CSF has no activity of accelerating platelet counts. Accordingly, even if one of ordinary skill in the art were motivated by the art to combine Washizuka with Ono or Ishikawa disclosing PEGylated hG-CSF, which the applicants do not believe would have been the case, it is apparent that the presently claimed invention, which uses chemically modified G-CSF, provides an unexpected effect.

Also, even if one of ordinary skill in the art were motivated by the art to combine the Background art of the present specification with Ono or Ishikawa disclosing PEGylated hG-CSF, which the applicants do not believe would have been the case, it is apparent that the presently claimed invention, which uses chemically modified G-CSF, provides an unexpected effect.

The claims are submitted to be patentable over the cited combination of art.

The attached complete copies of Koike and Washizuka are listed on the attached PTO 1449 Form and no further fee is believed to be required for consideration of the complete references and return of an initialed copy of the PTO 1449 Form, pursuant to MPEP § 609, however the Examiner is authorized by the attached over sheet to charge the undersigned's Deposit Account No. 14-1140 for any missing or deficient fee. A written explanation of any such charge is requested however.

Also listed on the attached PTO 1449 Form is the three JP documents lined-through on one of the PTO 1449 Forms returned by the Examiner with the Office Action of July 22, 2004, with the comment "No English Translation". These documents however were cited in an International Search Report mailed June 13, 1995 in connection with PCT/JP95/00266 (copy attached), which is a parent of the present application. The alleged relevance of the cited documents is described in the Search Report. The Patent Office indicated in a Notice of Acceptance dated October 11, 1996 in the parent application Serial No. 08/696,988 (copy attached) that this International Search Report as well as the cited documents were received from the International Bureau. The applicants presume that, pursuant to MPEP § 609, the Examiner has already considered these documents from the parent application. The applicants now desire to have these documents listed on the face of any patent issuing from the present application and request, pursuant to MPEP § 609, that the Examiner return an initialed copy of the attached PTO 1449 Form as confirmation that these documents have been considered. No further fee is believed to be required for consideration and return of an initialed copy of the PTO 1449 Form, pursuant to MPEP § 609, however the Examiner is authorized by the attached over sheet to charge the undersigned's Deposit

Account No. 14-1140 for any missing or deficient fee. A written explanation of any such charge is requested however.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required.

Respectfully submitted,

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